REMARKS

Claims 1-31 are in this application, and claims 16-19 have been examined. Claims 16-19 have been amended to better claim the invention. The method steps have been imported from claim 1, from which claim 16 depends, and for improved clarity, the claims have been amended to specify that the alphaviral replicon particles encode a plurality of antigens corresponding to an expression library from an antigen source. Support is found in the Specification in the paragraph bridging pages 23-24, for example. None of the amendments made herein constitute the addition of new matter.

The Requirement for Restriction

The Patent Office has made the requirement for restriction under 35 U.S.C. 121 final, alleging that the claims embody two patentably distinct inventions. Applicants request the rejoinder of the withdrawn claims.

The Information Disclosure Statement

The Examiner has noted that the reference listing in the as-filed Specification at pages 48-49 is not a proper Information Disclosure Statement. Applicants hereby clarify that the listing in the Specification was meant to serve as a bibliography rather than an Information Disclosure Statement.

Further to the Information Disclosure Statements previously filed in this application, Applicants advise the Patent Office that USSN 10/734,609, filed December 12, 2003 and published as 2004/0166573, has issued as US Patent 7,078,218. This patent and the instant application are commonly assigned.

Applicants have cited the '218 patent and have provided its file history (without references) as part of an Information Disclosure filed herewith. Favorable consideration is respectfully requested.

The Rejections under 36 USC 112,second paragraph

Claims 17-19 have been rejected under 35 U.S.C. 112, second paragraph, as allegedly indefinite. Applicants respectfully traverse this rejection.

The Patent Office has alleged that claim 17-19 are unclear in the recitation of "derived from". It is said to be unclear as to the nature and number of steps required to obtain a derivative of an antigen of a particular organism. It is said that the term implies a number of different steps that may or may not result in a change in the functional characteristics of the antigen as present from the source.

Applicants believe that the wording of amended claims 17-19 is abundantly clear and definite to the reader of ordinary skill in the art. The amended claims do not recite "derived from". Accordingly, the withdrawal of this rejection is respectfully requested.

The Double Patenting Rejections

Claims 16 and 18-19 have been rejected on the ground of nonstatutory double patenting as allegedly unpatentable over claim 6 of US Patent 7,090,852. Applicants respectfully traverse this rejection.

In the interest of advancing prosecution and without acquiescing to the rejection, Applicants have amended the claims to incorporate the limitations of claim 1 and to clarify that "the plurality of alphaviral replicon nucleic acids encode a plurality of antigens corresponding to a nucleic acid expression library synthesized from an antigen source", with respect to the alphaviral replicon particle preparation.

Applicants respectfully submit that there is nothing in the claims of the cited patent which make obvious the presently claimed invention, which relies on a particular method to produce an alphavirus replicon particle preparation which encodes a plurality of antigens corresponding to an expression library from an antigen source of interest. In part, it is the salt wash step which allows the production of such an alphavirus replicon particle preparation which corresponds to an expression library.

In view of the foregoing and the amendments to the claims, the withdrawal of the rejection is respectfully requested.

Claims 16 and 18-19 have been rejected on the ground of nonstatutory double patenting as allegedly unpatentable over claims 2-3 and 8-9 of US Patent 6,783,939. Applicants respectfully traverse this rejection.

In the interest of advancing prosecution and without acquiescing to the rejection, Applicants have amended the claims to incorporate the limitations of claim 1 and to clarify that "the plurality of alphaviral replicon nucleic acids encode a plurality of antigens corresponding to a nucleic acid expression library synthesized from an antigen source", with respect to the alphaviral replicon particle preparation.

Applicants respectfully submit that there is nothing in the claims of the cited patent which make obvious the presently claimed invention, which relies on a particular method to produce an alphavirus replicon particle preparation which encodes a plurality of antigens corresponding to an expression library from an antigen source of interest. In part, it is the salt wash step which allows the

production of such an alphavirus replicon particle preparation which corresponds to an expression library. The claims of the cited patent are strictly limited to three specific HIV antigens, and they would not make obvious the claimed preparation corresponding to an expression library.

In view of the foregoing, the withdrawal of the rejection is respectfully requested.

Claims 16 and 18-19 have been rejected on the ground of nonstatutory double patenting as allegedly unpatentable over claims 1, 3-8, 10-15, 33-40, 44-49 and 51-77 of US Patent 6,521,235. Applicants respectfully traverse this rejection.

In the interest of advancing prosecution and without acquiescing to the rejection, Applicants have amended the claims to incorporate the limitations of claim 1 and to clarify that "the plurality of alphaviral replicon nucleic acids encode a plurality of antigens corresponding to a nucleic acid expression library synthesized from an antigen source", with respect to the alphaviral replicon particle preparation.

Applicants respectfully submit that there is nothing in the claims of the cited patent which make obvious the presently claimed invention, which relies on a particular method to produce an alphavirus replicon particle preparation which encodes a plurality of antigens corresponding to an expression library from an antigen source of interest. In part, it is the salt wash step which allows the production of such an alphavirus replicon particle preparation which corresponds to an expression library. The claims of the cited patent do not indicate that the population of particles corresponds to an expression library, as set forth in the

present application. Note the dependent claims that appear to indicate a single immunogen (or fragment).

In view of the foregoing, the withdrawal of the rejection is respectfully requested.

Claims 16 and 18-19 have been rejected on the ground of nonstatutory double patenting as allegedly unpatentable over claims 32, 34-35, 37, 40, 42, 44-45, 47, 50-52, 54-55, 57, 60, 62, 64-65, 67, 72, 74-75, 77, 80, 82 and 84-90 of US Patent 6,531,135. Applicants respectfully traverse this rejection.

In the interest of advancing prosecution and without acquiescing to the rejection, Applicants have amended the claims to incorporate the limitations of claim 1 and to clarify that "the plurality of alphaviral replicon nucleic acids encode a plurality of antigens corresponding to a nucleic acid expression library synthesized from an antigen source", with respect to the alphaviral replicon particle preparation.

Applicants respectfully submit that there is nothing in the claims of the cited patent which make obvious the presently claimed invention, which relies on a particular method to produce an alphavirus replicon particle preparation which encodes a plurality of antigens corresponding to an expression library from an antigen source of interest. In part, it is the salt wash step which allows the production of such an alphavirus replicon particle preparation which corresponds to an expression library. The claims of the cited patent do not indicate that the population of particles corresponds to an expression library from an antigen source of interest, as set forth in the present application and claims. Note that the claims of the cited patent appear to indicate that there can be more than one

antigen expressed from a single alphavirus nucleic acid, but not that the population encodes antigens corresponding to an expression library from an antigen source of interest, as in the present application.

In view of the foregoing, the withdrawal of the rejection is respectfully requested.

Claims 16 and 18-19 have been rejected on the ground of nonstatutory double patenting as allegedly unpatentable over claims 1-13, 16-17, 19, 23-35, 37-55, 57 and 61 of US Patent 6,156,558. Applicants respectfully traverse this rejection.

In the interest of advancing prosecution and without acquiescing to the rejection, Applicants have amended the claims to incorporate the limitations of claim 1 and to clarify that "the plurality of alphaviral replicon nucleic acids encode a plurality of antigens corresponding to a nucleic acid expression library synthesized from an antigen source", with respect to the alphaviral replicon particle preparation.

Applicants respectfully submit that there is nothing in the claims of the cited patent which make obvious the presently claimed invention, which relies on a particular method to produce an alphavirus replicon particle preparation which encodes a plurality of antigens corresponding to an expression library from an antigen source of interest. In part, it is the salt wash step which allows the production of such an alphavirus replicon particle preparation which corresponds to an expression library. The claims of the cited patent do not indicate that the population of particles corresponds to an expression library from an antigen source of interest, as set forth in the present application and claims. Note that

the claims of the cited patent appear to indicate that there can be two antigens expressed from a single alphavirus nucleic acid, but not that the population encodes antigens corresponding to an expression library from an antigen source of interest, as in the present application.

In view of the foregoing, the withdrawal of the rejection is respectfully requested.

Claims 16 and 18-19 have been rejected on the ground of nonstatutory double patenting as allegedly unpatentable over claims 22-26, 28-29, 31-34 and 36-37 of US Patent 6,541,010. Applicants respectfully traverse this rejection.

In the interest of advancing prosecution and without acquiescing to the rejection, Applicants have amended the claims to incorporate the limitations of claim 1 and to clarify that "the plurality of alphaviral replicon nucleic acids encode a plurality of antigens corresponding to a nucleic acid expression library synthesized from an antigen source", with respect to the alphaviral replicon particle preparation.

Applicants respectfully submit that there is nothing in the claims of the cited patent which make obvious the presently claimed invention, which relies on a particular method to produce an alphavirus replicon particle preparation which encodes a plurality of antigens corresponding to an expression library from an antigen source of interest. In part, it is the salt wash step which allows the production of such an alphavirus replicon particle preparation which corresponds to an expression library. The claims of the cited patent do not indicate that the population of particles corresponds to an expression library from an antigen source of interest, as set forth in the present application and claims.

In view of the foregoing, the withdrawal of the rejection is respectfully requested.

Claims 16-19 have been provisionally rejected on the ground of nonstatutory obviousness-type double patenting as allegedly unpatentable over claims 1-21 of copending US Application 10/517,083. Applicants respectfully traverse this rejection.

As a first matter, Applicants respectfully submit that because the cited application is pending and has not been examined, the Patent Office should defer the rejection in the present application and should reinstitute the rejection if and when the cited application issues as a patent.

In the interest of advancing prosecution and without acquiescing to the rejection, Applicants have amended the claims to incorporate the limitations of claim 1 and to clarify that "the plurality of alphaviral replicon nucleic acids encode a plurality of antigens corresponding to an expression library for an antigen source", with respect to the alphaviral replicon particle preparation.

In any case, Applicants respectfully submit that there is nothing in the claims of the cited patent application which make obvious the presently claimed invention, which relies on a particular method to produce an alphavirus replicon particle preparation which encodes a plurality of antigens corresponding to an expression library from an antigen source of interest. In part, it is the salt wash step which allows the production of such an alphavirus replicon particle preparation which corresponds to an expression library. The claims of the cited patent application do not indicate that the population of particles corresponds to

an expression library from an antigen source of interest, as set forth in the present application and claims. Note that the claims of the cited application appear to indicate that there can be more than one antigen expressed from a single alphavirus nucleic acid, but not that the population encodes antigens corresponding to an expression library from an antigen source of interest, as in the present application.

With respect to the statement that the instantly rejected claims are obvious over the claims and specification of the other application, Applicants respectfully note that the specification is not properly used in the formulation of a rejection for allegedly obviousness-type double patenting.

In view of the foregoing, the withdrawal of the rejection is respectfully requested.

Claims 16 and 18-19 have been provisionally rejected on the ground of nonstatutory double patenting as allegedly unpatentable over claims 2-9, 17-18, and 23-26 of US Application 10/929,234. Applicants respectfully traverse this rejection.

In the interest of advancing prosecution and without acquiescing to the rejection, Applicants have amended the claims to incorporate the limitations of claim 1 and to clarify that "the plurality of alphaviral replicon nucleic acids encode a plurality of antigens corresponding to a nucleic acid expression library synthesized from an antigen source", with respect to the alphaviral replicon particle preparation.

Applicants respectfully submit that there is nothing in the claims of the cited patent which make obvious the presently claimed invention, which relies on a particular method to produce an alphavirus replicon particle preparation which encodes a plurality of antigens corresponding to an expression library from an antigen source of interest. In part, it is the salt wash step which allows the production of such an alphavirus replicon particle preparation which corresponds to an expression library. The claims of the cited patent do not indicate that the population of particles corresponds to an expression library from an antigen source of interest, as set forth in the present application and claims. Note that the claims of the cited application appear to indicate that there can be at most three antigens derived from HIV, but not that the population encodes antigens corresponding to an expression library from an antigen source of interest, as in the present application.

In view of the foregoing, the withdrawal of the rejection is respectfully requested.

Claims 16-19 have been provisionally rejected on the ground of nonstatutory double patenting as allegedly unpatentable over claims 18, 24 and 25 of copending US Application 11/132,711. Applicants respectfully traverse this rejection.

In the interest of advancing prosecution and without acquiescing to the rejection, Applicants have amended the claims to incorporate the limitations of claim 1 and to clarify that "the plurality of alphaviral replicon nucleic acids encode a plurality of antigens corresponding to a nucleic acid expression library synthesized from an antigen source", with respect to the alphaviral replicon particle preparation.

Applicants respectfully request that the Patent Office defer this rejection until one of these patent applications issues as a patent. This application is commonly owned, and Applicants agree to file a Terminal Disclaimer, if necessary, if the cited application were to be issued before the instant application.

In view of the foregoing, the withdrawal of the rejection is respectfully requested.

The Rejections under 35 U.S.C. 102

Claims 16 and 18-19 have been rejected as allegedly anticipated by US Patent 6,521,235 (Johnston et al.). Applicants respectfully traverse this rejection.

In the interest of advancing prosecution and without acquiescing to the rejection, Applicants have amended the claims to incorporate the method steps from base claim 1 and to specify that the population of alphavirus replicon particles encodes antigens corresponding to an expression library from an antigen source of interest. An important aspect of the method used to produce the population of the present invention as claimed is the salt wash step, which allows one to obtain dramatically larger alphavirus replicon particle yields than was possible in prior art methods; this, at least in part, allows the production of a representative expression library, rather than one containing only the most abundantly expressed proteins from an antigen source of interest. Specifically, in the '235 patent, yields of ARPs in BHK cells were reported to range from 3×10^5 to 1×10^8 per ml (Column 15, line 43). Applicants found that yields from the methods taught in the '235 patent in Vero cells were the same or less than those obtained in BHK cells. In contrast, Applicants'method produced yields on the

order of $10^{10} - 10^{11}$ (see Tables 1 and 2; paragraph [0056]), which are 2-3 orders of magnitude larger than the method practiced in the '235 patent. This is taught nowhere in the cited patent.

With respect to the allegation that the present inventors did not invent the claimed subject matter herein, Applicants state on the record that they are the inventors for the presently claimed subject matter, as attested in the Inventors' Declaration accepted in this application.

In view of the foregoing, the instant claimed invention is not properly rejected under Section 102(e) or (f). Thus, Applicants respectfully request the withdrawal of this rejection.

Claims 16 and 18-19 have been rejected as allegedly anticipated by US Patent 7,090,852 (Hevey et al.). Applicants respectfully traverse this rejection.

In the interest of advancing prosecution and without acquiescing to the rejection, Applicants have amended the claims to incorporate the method steps from base claim 1 and to specify that the population of alphavirus replicon particles encodes antigens corresponding to an expression library from an antigen source of interest. An important aspect of the method used to produce the population of the present invention as claimed is the salt wash step, which allows one to obtain dramatically larger alphavirus replicon particle yields than was possible in prior art methods; this, at least in part, allows the production of a representative expression library, rather than one containing only the most abundantly expressed proteins from an antigen source of interest. This is taught nowhere in the cited patent. Hevey et al. cited the 1997 publication of Pushko et al. for methods of packaging replicons into ARPs. This is the same method used

by Johnston et al. ('235 patent discussed above) that resulted in yields that are orders of magnitudes lower than those claimed herein.

In addition, the cited patent appears to be limited to antigens related to Marburg virus, while the present application relates to a wide variety of antigen sources. The cited patent does not appear to teach or suggest a mixed population of alphavirus replicon particles, but rather single antigen-expressing populations or a population consisting of particles in which several antigens are expressed from a single nucleic acid. With respect to paragraph 5 in col. 7, it is not the same to say one or more particles derived from one or more replicon nucleic acids encoding one or more Marburg virion proteins. This is not what is claimed in the present invention, and nowhere does the cited patent appear to teach the creation of an expression library in alphavirus replicon particles using the methods incorporated into the claims.

In view of the foregoing, the instant claims as amended are not properly rejected under Section 102(e). Thus, Applicants respectfully request the withdrawal of this rejection.

Claims 16 and 18-19 have been rejected under 35 U.S.C. 102(e) as allegedly anticipated by US Patent 6,783,939 (Olmsted). Applicants respectfully traverse this rejection.

The Patent Office has referred to claims 2-3 and 8-9 of the cited patent as indicating that it teaches compositions of alphavirus replicon particles, comprising one or more encoded antigens from gag, pol and env.

In the interest of advancing prosecution and without acquiescing to the rejection, Applicants have amended the claims to incorporate the method steps from base claim 1 and to specify that the population of alphavirus replicon particles encodes antigens corresponding to an expression library from an antigen source of interest. An important aspect of the method used to produce the population of the present invention as claimed is the salt wash step, which allows one to obtain dramatically larger alphavirus replicon particle yields than was possible in prior art methods; this, at least in part, allows the production of a representative expression library, rather than one containing only the most abundantly expressed proteins from an antigen source of interest. This is taught nowhere in the cited patent. Olmsted et al. teach a composition that comprises no more than three antigens, and these are specific clones that have been previously isolated and at least one of these antigens is modified in vitro from its native form, i.e. the form as it would appear in any expression library.

In view of the foregoing, Applicants respectfully maintain that the cited patent does not anticipate the instant invention as presently claimed, and the rejection must be withdrawn.

Claims 16 and 18-19 have been rejected under 35 U.S.C. 102(e) as allegedly anticipated by US Patent 6,521,235 (Johnston et al.). Applicants respectfully traverse this rejection.

The Patent Office has stated that claims 3-4 of the cited patent relate to alphavirus replicon vectors that encode one or more antigens and may be of viral, protozoan or bacterial origin.

In the interest of advancing prosecution and without acquiescing to the rejection, Applicants have amended the claims to incorporate the method steps from base claim 1 and to specify that the population of alphavirus replicon particles encodes antigens corresponding to an expression library from an antigen source of interest. An important aspect of the method used to produce the population of the present invention as claimed is the salt wash step, which allows one to obtain dramatically larger alphavirus replicon particle yields than was possible in prior art methods; this, at least in part, allows the production of a representative expression library, rather than one containing only the most abundantly expressed proteins from an antigen source of interest. This is taught nowhere in the cited patent, and the methods taught by Johnston et al. (as discussed hereinabove) do not provide sufficient yield to enable, let alone anticipate the present invention as claimed. At Column 8, line 61 through Column 9, line 8, Johnston et al. describe how they would accomplish vaccination with "two immunogens", which consists of two immunogens operably linked to separate control elements (i.e. a promoter or an IRES) included in a single replicon. This is not a strategy that would be feasible for expressing a library of nucleic acids.

In view of the foregoing, Applicants respectfully maintain that the cited patent does not anticipate the instant invention as presently claimed, and the rejection must be withdrawn.

Claims 16 and 18-19 have been rejected under 35 U.S.C. 102(e) as allegedly anticipated by US Patent 6,531,135 (Johnston et al.). Applicants respectfully traverse this rejection.

The Patent Office has stated that the cited patent teaches alphaviral replicon particles encoding more than one antigen (claims 34-35) which may be from several viral sources (e.g, col. 5). Applicants note that the '135 patent is a continuation of the issued '235 patent discussed hereinabove, and claims 34-35 of the '135 patent are analogous to claims 3-4 of the '235 patent, and the specifications are identical. Thus, the arguments made above with respect to the '235 patent apply directly to this rejection.

In the interest of advancing prosecution and without acquiescing to the rejection, Applicants have amended the claims to incorporate the method steps from base claim 1 and to specify that the population of alphavirus replicon particles encodes antigens corresponding to an expression library from an antigen source of interest. An important aspect of the method used to produce the population of the present invention as claimed is the salt wash step, which allows one to obtain dramatically larger alphavirus replicon particle yields than was possible in prior art methods; this, at least in part, allows the production of a representative expression library, rather than one containing only the most abundantly expressed proteins from an antigen source of interest. This is taught nowhere in the cited patent. The cited portion of the Johnston et al. patent teaches nothing about an expression library or the recited method of making such a population of alphavirus replicon particles.

In view of the foregoing, Applicants respectfully maintain that the cited patent does not anticipate the instant invention as presently claimed, and the rejection must be withdrawn.

Claims 16 and 18-19 have been rejected under 35 U.S.C. 102(a) as allegedly anticipated by US Patent 6,495,143 and US 2002/0034521 (Lee et al.). Applicants respectfully traverse this rejection.

The Patent Office has stated that the cited patent teaches alphaviral replicon particles encoding a plurality of botulinum bacteria antigens (e.g, claim 28).

In the interest of advancing prosecution and without acquiescing to the rejection, Applicants have amended the claims to incorporate the method steps from base claim 1 and to specify that the population of alphavirus replicon particles encodes antigens corresponding to an expression library from an antigen source of interest. An important aspect of the method used to produce the population of the present invention as claimed is the salt wash step, which allows one to obtain dramatically larger alphavirus replicon particle yields than was possible in prior art methods; this, at least in part, allows the production of a representative expression library, rather than one containing only the most abundantly expressed proteins from an antigen source of interest. This is taught nowhere in the cited patent. Applicants note that the cited claim includes a maximum of 6 encoded antigens, which is nowhere near a representative library of an antigen source such as *Clostridium botulinum*, a tumor or a pathogenic microorganism.

In view of the foregoing, Applicants respectfully maintain that the cited patent does not anticipate the instant invention as presently claimed, and the rejection must be withdrawn.

Claims 16 and 18-19 have been rejected under 35 U.S.C. 102(e) as allegedly anticipated by US Patent 6,632,640 (Lee et al.). Applicants respectfully traverse this rejection.

The Patent Office has stated that the cited patent teaches alphaviral replicon particles encoding two distinct antigens of *Staphylococcus aureus* exotoxins [sic] (e.g, col. 3, paragraphs 2-3).

In the interest of advancing prosecution and without acquiescing to the rejection, Applicants have amended the claims to incorporate the method steps from base claim 1 and to specify that the population of alphavirus replicon particles encodes antigens corresponding to an expression library from an antigen source of interest. An important aspect of the method used to produce the population of the present invention as claimed is the salt wash step, which allows one to obtain dramatically larger alphavirus replicon particle yields than was possible in prior art methods; this, at least in part, allows the production of a representative expression library, rather than one containing only the most abundantly expressed proteins from an antigen source of interest. This is taught nowhere in the cited patent. Applicants note that the cited passage appears to relate to two encoded antigens, which is nowhere near a representative library of an antigen source such as *Staphylococcus aureus*, a tumor or a pathogenic microorganism.

In view of the foregoing, Applicants respectfully maintain that the cited patent does not anticipate the instant invention as presently claimed, and the rejection must be withdrawn.

Claims 16 and 18-19 have been rejected under 35 U.S.C. 102(e) as allegedly anticipated by US Patent 6,770,479 (Lee et al.). Applicants respectfully traverse this rejection.

The Patent Office has stated that the cited patent teaches a composition of VEE replicons encoding more than one antigen of anthrax (e.g, claim 15).

In the interest of advancing prosecution and without acquiescing to the rejection, Applicants have amended the claims to incorporate the method steps from base claim 1 and to specify that the population of alphavirus replicon particles encodes antigens corresponding to an expression library from an antigen source of interest. An important aspect of the method used to produce the population of the present invention as claimed is the salt wash step, which allows one to obtain dramatically larger alphavirus replicon particle yields than was possible in prior art methods; this, at least in part, allows the production of a representative expression library, rather than one containing only the most abundantly expressed proteins from an antigen source of interest. This is taught nowhere in the cited patent. Applicants note that the cited claim appears to relate to four encoded antigens, which is nowhere near a representative library of an antigen source such as *Bacillus anthracis*, a tumor or a pathogenic microorganism.

In view of the foregoing, Applicants respectfully maintain that the cited patent does not anticipate the instant invention as presently claimed, and the rejection must be withdrawn.

Claims 16 and 18-19 have been rejected under 35 U.S.C. 102(a) as allegedly anticipated by US Publication 2002/0164582 (Hart et al.). Applicants respectfully traverse this rejection.

The Patent Office has stated that the cited patent teaches a composition of VEE replicons encoding antigens of Ebola virus (e.g, claim 59 and paragraph 0025).

In the interest of advancing prosecution and without acquiescing to the rejection, Applicants have amended the claims to incorporate the method steps from base claim 1 and to specify that the population of alphavirus replicon particles encodes antigens corresponding to an expression library from an antigen source of interest. An important aspect of the method used to produce the population of the present invention as claimed is the salt wash step, which allows one to obtain dramatically larger alphavirus replicon particle yields than was possible in prior art methods; this, at least in part, allows the production of a representative expression library, rather than one containing only the most abundantly expressed proteins from an antigen source of interest. This is taught nowhere in the cited patent. Applicants note that the cited paragraph 25 refers to a limited number of encoded antigens (paragraph 0013 appears to refer to 6), which is not believed to be a representative library of an antigen source such as Ebola virus, a tumor or a pathogenic microorganism.

In view of the foregoing, Applicants respectfully maintain that the cited patent does not anticipate the instant invention as presently claimed, and the rejection must be withdrawn.

Claims 16 and 18-19 have been rejected under 35 U.S.C. 102(e) as allegedly anticipated by US Patent 6,517,842 (Hevey et al.). Applicants respectfully traverse this rejection.

The Patent Office has stated that the cited patent teaches a composition of VEE replicons encoding more than one antigen of Marburg virus (e.g., col. 3, paragraph 4).

In the interest of advancing prosecution and without acquiescing to the rejection, Applicants have amended the claims to incorporate the method steps from base claim 1 and to specify that the population of alphavirus replicon particles encodes antigens corresponding to an expression library from an antigen source of interest. An important aspect of the method used to produce the population of the present invention as claimed is the salt wash step, which allows one to obtain dramatically larger alphavirus replicon particle yields than was possible in prior art methods; this, at least in part, allows the production of a representative expression library, rather than one containing only the most abundantly expressed proteins from an antigen source of interest. This is taught nowhere in the cited patent. Applicants note that the cited claim appears to relate to seven encoded proteins, which is not believed to be a representative library of an antigen source such as Marburg virus, a tumor or a pathogenic microorganism.

In view of the foregoing, Applicants respectfully maintain that the cited patent does not anticipate the instant invention as presently claimed, and the rejection must be withdrawn.

Claims 16 and 18-19 have been rejected under 35 U.S.C. 102(e) as allegedly anticipated by US Patent 6,156,558 (Johnston et al.). Applicants respectfully traverse this rejection.

The Patent Office has stated that the cited patent teaches a plurality of alphavirus particles encoding a plurality of antigens (e.g, col. 5).

In the interest of advancing prosecution and without acquiescing to the rejection, Applicants have amended the claims to incorporate the method steps from base claim 1 and to specify that the population of alphavirus replicon particles encodes antigens corresponding to an expression library from an antigen source of interest. An important aspect of the method used to produce the population of the present invention as claimed is the salt wash step, which allows one to obtain dramatically larger alphavirus replicon particle yields than was possible in prior art methods; this, at least in part, allows the production of a representative expression library, rather than one containing only the most abundantly expressed proteins from an antigen source of interest. This is taught nowhere in the cited patent. Applicants note that the cited passage appears to relate to certain viruses, but it does not appear to teach or suggest that encoded antigens corresponding to a representative library of an antigen source is incorporated into a population of alphavirus replicon particles using the methodology recited in the instant claims.

In view of the foregoing, Applicants respectfully maintain that the cited patent does not anticipate the instant invention as presently claimed, and the rejection must be withdrawn.

Claims 16 and 18-19 have been rejected under 35 U.S.C. 102(e) as allegedly anticipated by US Patent 6,451,592 (Dubensky et al.). Applicants respectfully traverse this rejection.

The Patent Office has stated that the cited patent teaches a composition of alphavirus replicons comprising multiple heterologous sequences (e.g., col. 3, paragraph 4; cols. 33-34, bridging paragraph).

In the interest of advancing prosecution and without acquiescing to the rejection, Applicants have amended the claims to incorporate the method steps from base claim 1 and to specify that the population of alphavirus replicon particles encodes antigens corresponding to an expression library from an antigen source of interest. An important aspect of the method used to produce the population of the present invention as claimed is the salt wash step, which allows one to obtain dramatically larger alphavirus replicon particle yields than was possible in prior art methods; this, at least in part, allows the production of a representative expression library, rather than one containing only the most abundantly expressed proteins from an antigen source of interest. This is taught nowhere in the cited patent. It appears to Applicants that the cited paragraph relates to a single alphaviral nucleic acid molecule engineered to express more than one antigen or nucleic acid. The context does not teach or suggest a population corresponding to an expression library. The second cited paragraph similarly appears to lack such a teaching.

In view of the foregoing, Applicants respectfully maintain that the cited patent does not anticipate the instant invention as presently claimed, and the rejection must be withdrawn.

Claims 16 and 18-19 have been rejected under 35 U.S.C. 102(e) as allegedly anticipated by US Patent 5,792,462 (Johnston et al.). Applicants respectfully traverse this rejection.

The Patent Office has stated that the cited patent teaches a composition of VEE replicons encoding more than one Lassa fever virus protein (Example 4).

In the interest of advancing prosecution and without acquiescing to the rejection, Applicants have amended the claims to incorporate the method steps from base claim 1 and to specify that the population of alphavirus replicon particles encodes antigens corresponding to an expression library from an antigen source of interest. An important aspect of the method used to produce the population of the present invention as claimed is the salt wash step, which allows one to obtain dramatically larger alphavirus replicon particle yields than was possible in prior art methods; this, at least in part, allows the production of a representative expression library, rather than one containing only the most abundantly expressed proteins from an antigen source of interest. This is taught nowhere in the cited patent. It appears to Applicants that the cited Example (4) relates to coding sequences separately cloned into a VEE replicon nucleic acid, and the introduction of an alphaviral nucleic acid molecule encoding a single Lassa fever antigen (with two helper nucleic acids) into MHK cells. The Lassa fever antigen-encoding preparation then was administered to mice, where an immune response was triggered. The context does not teach or suggest a population corresponding to an expression library.

In view of the foregoing, Applicants respectfully maintain that the cited patent does not anticipate the instant invention as presently claimed, and the rejection must be withdrawn.

The Rejections under 35 U.S.C. 103

Claims 16-17 have been rejected under 35 U.S.C. 103 as allegedly unpatentable over US Patent 6,156,558 (Johnston), Nestle et al. (1998) and Smooker (2000). Applicants respectfully traverse this rejection.

The cited Johnston reference is said to teach the use of similar alphavirus particles in vaccines and to demonstrate that particles are sufficient to produce immune responses against foreign gene encoded proteins, but Johnston is acknowledged to lack the teaching of a plurality of antigens or the use of cancer antigens.

Nestle is said to teach a cocktail of peptides used to produce cancer immunity and Smooker is said to demonstrate that a library of epitopes may be administered to develop an immune response. The Patent Office has concluded that it would have been obvious to make a plurality of alphaviral replicons encoding the different peptides of Nestle and that the artisan would have been motivated to do so to produce an immune response to cancer, using the method of Smooker instead of actual delivery of the polypeptides. It is also alleged that there would have been a reasonable expectation of success as Smooker had demonstrated that a plurality of antigens could have been delivered and Nestle taught that the plurality of peptides produced immune response to cancer.

In the interest of advancing prosecution and without acquiescing to the rejection, Applicants have amended the claims to incorporate the method steps from base claim 1 and to specify that the population of alphavirus replicon particles encodes antigens corresponding to an expression library from an antigen source of interest. An important aspect of the method used to produce

the population of the present invention as claimed is the salt wash step, which allows one to obtain dramatically larger alphavirus replicon particle yields than was possible in prior art methods; this, at least in part, allows the production of a representative expression library, rather than one containing only the most abundantly expressed proteins from an antigen source of interest.

The Smooker reference teaches the creation of a secreted peptide expression library to be administered as a DNA preparation; at page 2535 it is stated that the majority of in-frame peptides were less than 20 amino acids and 13% were greater than 50 amino acids, with a range from 1-115. Thus, the library is one of partial proteins, and by virtue of the necessity for in frame fusions, only 1 in 6 clones represents a portion of a protein expressed in the antigen source (i.e. Plasmodium). This is a very different approach than is taken in the present Specification or is claimed in this application.

The cited Nestle reference relates to vaccination of melanoma patients with peptide or tumor lysate pulsed dendritic cells. This reference does not teach or suggest the use of any sort of expression library for immunizing a patient.

Combining the cited references, in the absence of hindsight could give a DNA vector for expressing melanoma antigens, an alphavirus system for expressing a plasmodium peptide library, a lysate of plasmodium or single preparations for expressing hemagglutinin, green fluorescent protein, or Lassa fever N antigen or the proteins themselves. There is nothing that would point the way to the present claimed invention, especially in view of the relatively low recovery of the alphavirus replicon particles prior to present Applicants' discovery of the dramatic increase in yield with the use of a salt wash for alphavirus particles which are characterized by heparin binding.

In view of the foregoing, Applicants respectfully submit that the invention as claimed is not prima facie obvious over the cited art, and the withdrawal of the rejection is requested.

Claims 16 and 18-19 have been rejected under 35 U.S.C. 103 as allegedly unpatentable over US Patent 6,156,558 (Johnston) and Smooker (2000). Applicants respectfully traverse this rejection.

Johnston is said to have taught the use of similar alphaviral particles in vaccines and that the particles are sufficient to produce immune responses against foreign gene encoded proteins, but Johnston is acknowledged not to teach the use of a plurality of antigens or the use of antigens to protozoans. Smooker is said to teach a library of epitopes expressed on separate plasmids (a library) for immunizing mice against Plasmodium, a protozoan. The Patent Office has concluded that it would have been obvious to make a library of alphavirus replicon particles encoding different foreign antigens of the protozoan, that the artisan would have been motivated to do so to immunize mice and that there would have been a reasonable expectation of success.

In the interest of advancing prosecution and without acquiescing to the rejection, Applicants have amended the claims to incorporate the method steps from base claim 1 and to specify that the population of alphavirus replicon particles encodes antigens corresponding to an expression library from an antigen source of interest. An important aspect of the method used to produce the population of the present invention as claimed is the salt wash step, which allows one to obtain dramatically larger alphavirus replicon particle yields than was possible in prior art methods; this, at least in part, allows the production of a representative expression library, rather than one containing only the most abundantly expressed proteins from an antigen source of interest.

In view of the foregoing, Applicants submit that the presently claimed invention is not prima facie obvious over the cited references, and the withdrawal is respectfully requested.

Claims 16 and 18-19 have been rejected under 35 U.S.C. 103 as allegedly unpatentable over US Patent 6,235,290 (Brunham), US Patent 6,156,558 (Johnston) and Smooker (2000). Applicants respectfully traverse this rejection.

Brunham is said to teach a DNA vaccine against Chlamydia and the design of a multivalent vaccine using various forms of the MOMP gene to provide increased immunity of more strains of Chlamydia. Johnston is said to teach the use of similar alphavirus replicon particles in vaccines and that the particles are sufficient to produce an immune response against foreign gene encoded proteins. Smooker is said to teach a library of Plasmodium epitopes expressed via a plasmid library. The Patent Office has concluded that it would have been obvious to modify the Brunham composition to contain MOMP antigens in the Johnston vectors, that there was motivation to increase the number of Chlamydia strains to which an immune response is elicited and that the artisan would have had reasonable expectation of success as Smooker had taught that large libraries of peptides elicited immunity when administered as a DNA vaccine.

The cited Johnston and Smooker references have been discussed above. The Brunham reference does not teach the need for immunizing with more than one protein from the antigen source, i.e., a major outer membrane protein from Chlamydia. Based on the teachings of the three cited references, it would be more likely that one of ordinary skill in the art would have been motivated to express the MOMP in an alphavirus or to make an epitope library using the

MOMP coding sequence(s) as starting materials. Brunham teaches that a "possibly more feasible way is to design a multivalent vaccine based on multiple MOMP genes". Since Brunham only teaches a single MOMP gene on each DNA molecule, the only permissible inference of the suggestion of Brunham is to construct several different DNA vectors, each capable of expressing a different MOMP gene and then make a cocktail of these individually selected and synthesized DNA vectors. This approach was acknowledged by Applicants in the instant application as encompassed in the existing art and is quite distinct from the invention as currently claimed. Applicants do not see that it would have been obvious to make a representative expression library using alphavirus replicon particles based on these references. In addition, as noted above, prior art methods for collecting alphavirus particles did not allow for the improved yields only enabled in the present disclosure (and in US Patent 7,078,218, filed on even date herewith and commonly assigned). A critical step is the salt wash for collecting the alphaviral particles which are characterized by the ability to bind heparin.

In the interest of advancing prosecution and without acquiescing to the rejection, Applicants have amended the claims to incorporate the method steps from base claim 1 and to specify that the population of alphavirus replicon particles encodes antigens corresponding to an expression library from an antigen source of interest. An important aspect of the method used to produce the population of the present invention as claimed is the salt wash step, which allows one to obtain dramatically larger alphavirus replicon particle yields than was possible in prior art methods; this, at least in part, allows the production of a representative expression library, rather than one containing only the most abundantly expressed proteins from an antigen source of interest.

The cited Brunham patent teaches DNA immunization as a means to elicit an immune response, in particular to a major outer membrane protein of Chlamydia. There is no teaching of a variety of antigens (only fragments or variations of the particular chlamydial MOMP). In that Brunham teaches a distinct approach (DNA immunization, single target antigen) from that of the present claimed invention (alphavirus replicon particle, representative expression library, preparation made in a particular high efficiency way, i.e., with salt wash to significantly increase particle yield), the cited Brunham reference should be viewed as teaching away from the present claimed invention. Similarly, Smooker teaches away from the present claimed invention in that there is a peptide epitope plasmid library. Johnston, with its teaching of a limited teaching of alphavirus replicon particles and immune responses, would not appear to trump the alternate approaches of Brunham and Smooker in the absence of the impermissible use of hindsight.

In view of the foregoing, Applicants respectfully maintain that the present invention as claimed is not prima facie obvious over the cited references and request that the rejection should be withdrawn.

Claims 16-19 have been rejected under 35 U.S.C. 103 as allegedly unpatentable over US Patent 5,866,553 (Donnelly), US Patent 6,156,558 (Johnston) and Smooker (2000). Applicants respectfully traverse this rejection.

Donnelly is said to have taught immune responses to papilloma virus via DNA constructs encoding papilloma gene products. The patent office has concluded that because several antigens are taught which may be used in combination immunization was against cancer. Johnston is said to teach the use of similar alphavirus replicon particles in vaccines and that the particles are

sufficient to produce an immune response against foreign gene encoded proteins. Smooker is said to teach a library of Plasmodium epitopes expressed via a plasmid library. The Patent Office has concluded that it would have been obvious to modify the composition of Donnelly to contain different antigens of HPV in the alphaviruses of Johnston, that there was motivation to provide immunity to HPV and cancer and that the artisan would have had a reasonable expectation of success as Smooker had taught libraries of particles could elicit immunity.

In the interest of advancing prosecution and without acquiescing to the rejection, Applicants have amended the claims to incorporate the method steps from base claim 1 and to specify that the population of alphavirus replicon particles encodes antigens corresponding to an expression library from an antigen source of interest. An important aspect of the method used to produce the population of the present invention as claimed is the salt wash step, which allows one to obtain dramatically larger alphavirus replicon particle yields than was possible in prior art methods; this, at least in part, allows the production of a representative expression library, rather than one containing only the most abundantly expressed proteins from an antigen source of interest.

Donnelly appears to teach "monovalent and multivalent vaccines for preventing PV infection. The monovalent vaccine may be made by formulating DNA encoding HPV16 L1 protein or L2 protein, or L1 + L2 proteins. Alternatively, a multivalent HPV vaccine may be formulated by mixing DNA encoding L1 or L2 or L1+L2 proteins from different HPV types" . Thus, Donnelly at most teaches 2 selected antigens in a given construct and teaches making cocktails of different constructs to achieve "multivalent' vaccines. Smooker teaches the expression of peptide epitopes via a plasmid library. Both of these approaches are different from that of present Applicants, and thus can be considered to teach away from

the alphavirus replicon particle expression library approach. Johnston teaches the alphavirus replicon particle approach, but does not teach the use of the method steps recited in the claims as amended to prepare a particle preparation. These steps (notably the salt wash step) allow the production of a significantly larger number of particles from a comparable attempt and thus, the production of a representative expression library where the possible members are numerous. It is only by hindsight reconstruction that the Examiner could have selected various aspects from the cited references to arrive at the obviousness rejection. In addition, the particles of Smooker were biolistic particles with a DNA vector, not the alphavirus particles of the present invention, which actually are believed to allow for more efficient expression due to the ability of the virus envelope proteins to facilitate entry into cells. In addition, the viral proteins target the replicon nucleic acid to dendritic cells, thus further facilitating the development of an immune response.

Claims 16 and 18-19 have been rejected under 35 U.S.C. 103 as allegedly unpatentable over US Patent 6,309,642 (Cutler), US Patent 6,156,558 (Johnston) and Smooker (2000). Applicants respectfully traverse this rejection.

Cutler is said to teach several antigens designed to elicit immunity to Candida delivered by polynucleotides encoding the antigens. Johnston is said to teach the use of similar alphavirus replicon particles in vaccines and that the particles are sufficient to produce an immune response against foreign gene encoded proteins. Smooker is said to teach a library of Plasmodium epitopes expressed via a plasmid library. The Patent Office has concluded that it would have been obvious to modify the methods of Cutler by making several alphaviral replicon particles of Johnston to encode different antigens taught by Cutler, that there was motivation to provide immunity to Candida as Johnston taught such

DNA immunization would provide similar immunity and that the artisan would have had a reasonable expectation of success as Smooker had taught libraries of particles could elicit immunity.

In the interest of advancing prosecution and without acquiescing to the rejection, Applicants have amended the claims to incorporate the method steps from base claim 1 and to specify that the population of alphavirus replicon particles encodes antigens corresponding to an expression library from an antigen source of interest. An important aspect of the method used to produce the population of the present invention as claimed is the salt wash step, which allows one to obtain dramatically larger alphavirus replicon particle yields than was possible in prior art methods; this, at least in part, allows the production of a representative expression library, rather than one containing only the most abundantly expressed proteins from an antigen source of interest.

Applicants note that the Cutler patent teaches the use of **peptides** which mimic carbohydrate (mannan) epitopes from Candida as immunogens; see col. 4, lines 12-19. There is extensive disclosure related to the limited scope of this actual antigenic target in this patent. This appears to be a very specific subset of epitopes associated with Candida and not relevant to the invention as claimed in the present application. In Cutler the peptides are mimics of carbohydrate antigens – they do not correspond in structure to a naturally occurring antigen.

It is not believed that the teaching of Cutler combined with those of the other two references would lead one to the present claimed invention in the absence of the use of hindsight. Rather it might be likely that the encoded peptides might be presented as a DNA vaccine or a particular mimotope might be expressed by an alphavirus vector. In any case, there was no enabling

disclosure as to the particular method used to produce the alphaviral replicon particle preparation of the instant claimed invention with its salt wash step.

In view of the foregoing, Applicants respectfully maintain that claimed invention (as amended) is not prima facie obvious over the cited references, and the withdrawal of the rejection is requested.

Conclusion

In view of the foregoing, it is submitted that this case is in condition for allowance, and passage to issuance is respectfully requested.

If there are any outstanding issues related to patentability, the courtesy of a telephone interview is requested, and the Examiner is invited to call to arrange a mutually convenient time.

This amendment is accompanied by an Information Disclosure Statement and a Petition for Extension of Time (three months) with authorization to charge the amount of $1200.00, as required under 37 C.F.R. 1.17. It is believed that this response does not necessitate the payment of any additional fees under 37 C.F.R. 1.16-1.17 for extension and consideration of the Information Disclosure Statement. If the amount submitted is incorrect, however, please charge the necessary amount to Deposit Account No. 07-1969.

Respectfully submitted,

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